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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/572,711	03/20/2006	Gregg Bogosian	11916.0059.PC/US01	5263
45607 7590 10/17/2008 HOWREY LLP C/O IP DOCKETING DEPARTMENT 2941 FAIRVIEW PARK DRIVE SUITE 200 FALLS CHURCH, VA 22042				
EXAMINER				
PAK, YONG D				
ART UNIT		PAPER NUMBER		
1652				
MAIL DATE		DELIVERY MODE		
10/17/2008		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/572,711

**Applicant(s)**

BOGOSIAN ET AL.

**Examiner**

YONG D. PAK

**Art Unit**

1652

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-5, 8-18, 27-30, 32 and 34-48 is/are pending in the application.
- 4a) Of the above claim(s) 13, 27-30, 32, 34-41 and 44-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5, 8-12, 14-18, 42, 43, 47 and 48 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 March 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 6/16/08 & 3/20/06
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

This application is a 371 of PCT/US04/31224.

The amendment filed on July 21, 2008, amending claims 1-5, 9-10, 17, 27-29, 32, 34, 36-38, and 42, canceling claims 6-7, 19-26, 31, and 33 and adding claims 43-48, has been entered. No new matter has been entered.

Claims 1-5, 8-18, 27-30, 32, and 34-48 are pending. Claims 13, 27-30, 32, 34-41, and 44-46. Claims 1-5, 8-12, 14-18, 42-43, and 47-48 are under consideration.

### ***Election/Restrictions***

Applicant's election with traverse of Group I with a further election of SEQ ID NO:1 and bovine somatotropin in the reply filed on July 21, 2008 is acknowledged. The traversal is on the ground(s) that the requirement to elect a specific somatotropin should be withdrawn since the crux of the elected invention is the NSAA degrading enzyme. This is found persuasive and all heterologous proteins will be examined. The traversal is also on the ground(s) that claims 27-30, 32 and 35-41 of group III should be examined along with the claims of group I because the claims of Group III only differ from the group I claims by additionally reciting the isolation of the heterogously expressed protein and the claims sets from Group I and III are not mutually exclusive. This is not found persuasive because Group I and Group III are drawn to process claims having different utility and steps. According to Patent Rules 1.475, a national stage application containing claims to different categories of invention will be not considered to have unity of invention if the claims are drawn to multiple processes. The traversal is

also on the ground(s) that the claims should be examined for the method as it employs wildtype GDH (SEQ ID NO:2) or K92L GDH (SEQ ID NO:4). This is found persuasive and both SEQ ID NO:2 and 4 will be examined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 43 and 47 are partially directed to non-elected inventions (non-glutamate dehydrogenases). For examination purposes, the Examiner will only examine the elected invention, a method of using the glutamate dehydrogenase of SEQ ID NO:2 or 4.

#### ***Claim for Foreign Priority***

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The certified copy has been filed in the instant application.

#### ***Information Disclosure Statement***

The information disclosure statements (IDS) submitted on June 16, 2008 and March 20, 2006 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 12 and claim 4 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 12 recite the phrase "K92L" or "lysine 92 leucine". The metes and bounds of the above phrases are not clear in the context of the claims. The amino acid position corresponding to a specific position can be easily confused depending on how sequences are aligned. Therefore, it is unclear from the specification or from the claim as to what applicants mean by the above phrases. Examiner suggests direct reference to amino acid positions with a sequence identifier.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8-12, 14-18, 42-43, and 47-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 8-12, 14-18, 42-43, and 47-48 are drawn to a method of reducing the incorporation of non-standard amino acids into a heterologous protein in a microorganism by co-expressing in said microorganism said heterologous protein and a (A) non-standard amino acid degrading protein, (B) glutamate dehydrogenase, (C) K92L variant glutamate dehydrogenase from *E. coli*, (D) a sequence selected from SEQ ID NO:2 or 4 or is encoded by a DNA molecule having a sequence selected from SEQ ID NO:1 or 3. It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly interpreted "a sequence" to encompass a fragment of as few as 2 contiguous nucleic acids of SEQ ID NO:3 or 5 or 2 contiguous amino acids of SEQ ID NO:2 or 4. Further, the K92L variant of a glutamate dehydrogenase from *E. coli* is not limited to only the substitution at "92". Therefore, while the variant glutamate dehydrogenase comprises the recited substitution, the same variant glutamate dehydrogenase can comprise any amino acids in any other positions. Therefore, the claims are encompass a method of using (A) any or all non-standard amino acid degrading protein isolated from any or all source, including any or all mutants, recombinants and variants thereof, (B) any or all glutamate dehydrogenases, isolated from any or all source, including any or all mutants, recombinants and variants thereof, (C) any or all variants of a glutamate dehydrogenase from *E. coli* having a leucine residue at position "92", (D) any or all polypeptides having as little as two amino acids of SEQ ID NO:2 or 4 or encoded by a polynucleotide having as little as two nucleic acids of SEQ ID NO:1 or 3. Therefore, the claims are drawn to a method of using a genus of

polypeptides having non-standard amino acid degrading activity, but having unknown structure.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The recitation of "non-standard amino acid degrading" and "glutamate dehydrogenase" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in UC

California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "non-standard amino acid degrading" and "glutamate dehydrogenase" proteins, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Therefore, in the instant case, the claim is drawn to a method of using a genus of polypeptides having non-standard amino acid degrading activity, but having unknown structure. The specification only describes a method of reducing the incorporation of non-standard amino acids of a heterologous polypeptide produced by a microorganism by transforming into said microorganism a vector comprising said heterologous polypeptide and the glutamate dehydrogenase of SEQ ID NO:2 or 4. While MPEP 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by



disclosing only one species within the genus." In view of the widely variant species encompassed by the genus, this one example is not enough and does not constitute a representative number of species to describe the whole genus of any or all variants, recombinant and mutants of any or all polypeptides having non-standard amino acid degrading activity, including any or all variants, recombinants and mutants thereof, and there is no evidence on the record of the relationship between the structure of the non-standard amino acid degrading protein/glutamate dehydrogenase of SEQ ID NO:2 or 4 and the structure of any or all recombinant, variant and mutant of any or all polypeptides having non-standard amino acid degrading activity. Therefore, the specification fails to describe a representative species of the genus comprising any or all polypeptides having non-standard amino acid degrading activity, including any or all variants, recombinants and mutants thereof.

Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

Claims 1-5, 8-12, 14-18, 42-43, and 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the incorporation of non-standard amino acids of a heterologous polypeptide produced by a microorganism by transforming into said microorganism a vector comprising said heterologous polypeptide and the glutamate dehydrogenase of SEQ ID NO:2 or 4, does not reasonably provide enablement for a method of using any or all polypeptides having non-standard amino acid degrading activity, but having unknown structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-5, 8-12, 14-18, 42-43, and 47-48 are drawn to a method of reducing the incorporation of non-standard amino acids into a heterologous protein in a microorganism by co-expressing in said microorganism said heterologous protein and a (A) non-standard amino acid degrading protein, (B) glutamate dehydrogenase, (C) K92L variant glutamate dehydrogenase from *E. coli*, (D) a sequence selected from SEQ ID

NO:2 or 4 or is encoded by a DNA molecule having a sequence selected from SEQ ID NO:1 or 3.

***The breadth of the claims.***

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly interpreted "a sequence" to encompass a fragment of as few as 2 contiguous nucleic acids of SEQ ID NO:3 or 5 or 2 contiguous amino acids of SEQ ID NO:2 or 4. Further, the K92L variant of a glutamate dehydrogenase from *E. coli* is not limited to only the substitution at "92". Therefore, while the variant glutamate dehydrogenase comprises the recited substitution, the same variant glutamate dehydrogenase can comprise any amino acids in any other positions. Therefore, the claims are encompass a method of using (A) any or all non-standard amino acid degrading protein isolated from any or all source, including any or all mutants, recombinants and variants thereof, (B) any or all glutamate dehydrogenases, isolated from any or all source, including any or all mutants, recombinants and variants thereof, (C) any or all variants of a glutamate dehydrogenase from *E. coli* having a leucine residue at position "92", (D) any or all polypeptides having as little as two amino acids of SEQ ID NO:2 or 4 or encoded by a polynucleotide having as little as two nucleic acids of SEQ ID NO:1 or 3. Therefore, the claims are drawn to a method of using polypeptides having non-standard amino acid degrading activity, but having unknown structure.

Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of a method of using any or all polypeptides having non-standard amino acid degrading activity, but having unknown structure. In the instant case, the specification enables only a method of reducing the incorporation of non-standard amino acids of a heterologous polypeptide produced by a microorganism by transforming into said microorganism a vector comprising said heterologous polypeptide and the glutamate dehydrogenase of SEQ ID NO:2 or 4.

***The state of prior art, the relative skill of those in the art, and predictability or unpredictability of the art.***

Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within a non-standard amino acid degrading protein/glutamate dehydrogenase can be modified and which ones are conserved such that one of skill in the art can make the recited polypeptides having the same biological activity as that of the polypeptide of SEQ ID NO:2 or 4, (2) which segments of SEQ ID NO:2 or 4 are essential for activity,

and (3) the general tolerance of non-standard amino acid degrading protein/glutamate dehydrogenase to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions.

***The amount of direction or guidance presented and the existence of working examples.***

The specification discloses a method of reducing the incorporation of non-standard amino acids of a heterologous polypeptide produced by a microorganism by transforming into said microorganism a vector comprising said heterologous polypeptide and the glutamate dehydrogenase of SEQ ID NO:2 or 4. However, the specification fails to provide any information as to (1) specific substrates associated with any non-standard amino acid degrading protein/glutamate dehydrogenase isolated from any source, including variants, mutants and recombinants thereof, (2) structural elements

required in a polypeptide having non-standard amino acid degrading protein/glutamate dehydrogenase activity, or (3) which are the structural elements in a non-standard amino acid degrading protein/glutamate dehydrogenase that are essential to display non-standard amino acid degrading protein/glutamate dehydrogenase activity. No correlation between structure and function of having non-standard amino acid degrading protein/glutamate dehydrogenase activity has been presented. There is no information or guidance as to which amino acid residues in the polypeptides of SEQ ID NO:2 or 4 can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2 or 4.

***The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.***

While enzyme isolation techniques, recombinant and mutagenesis techniques were known in the art at the time of the invention, e.g. hybridization or mutagenesis, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, it is not routine in the art to create variants of polynucleotides encoding polypeptides having the activity

recited without any knowledge as to the structural features which would correlate with that activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of using any or all polypeptides having non-standard amino acid degrading activity, including variants, mutants, recombinants and fragments thereof. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any or all mutants, variants and recombinants of any or all polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 8-11, 14-18, 42-43, and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al., Bogosian et al. and Fenton et al.

Claims 1-2, 8-11, 14-18, 42-43, and 47-48 are drawn to a method of reducing the incorporation of non-standard amino acid, norleucine, into a bovine somatotropin in a microorganism by co-expressing in said microorganism said somatotropin and a non-standard amino acid degrading protein/glutamate dehydrogenase variant (K92L).

Wang et al. (Eur J Biochem. 2001 Nov;268(22):5791-9 – form PTO-892) discloses a mutant glutamate dehydrogenase isolated from *Clostridium symbiosum*, wherein said mutant has a K89L mutation and said mutant has increased activity for degrading norleucine (abstract, Table 4 on page 5796).

Bogosian et al. (US Patent No. 5,932,439 – form PTO-892) discloses expression and production of bovine somatotropin (Column 8, lines 27-51).

The difference between the above references and the instant invention is that the above references do not teach a method of using the mutant of Wang et al. in a method of reducing the incorporation of norleucine in bovine somatotropin.



However, it is well known in the art that that production of heterologous proteins in *E. coli* is hampered by incorporation of non-standard amino acids such as norleucine (Fenton et al. – US Patent No. 5,599,690 – form PTO-892, Column 1).

Therefore, combining the teachings of Wang et al., Bogosian et al. and Fenton et al., it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to reduce the incorporation of norleucine in production of heterologous proteins, such as bovine somatotropin, in *E. coli*, by transforming *E. coli* with a vector comprising said heterologous protein or bovine somatotropin of Bogosian et al. and the mutant of Fenton et al. or two vectors comprising each of the proteins.

One of ordinary skill in the art would have been motivated to combine the above references in order to reduce incorporation of norleucine when producing heterologous proteins in *E. coli*. One of ordinary skill in the art would have had a reasonable expectation of success since Wang et al. teaches a mutant enzyme which degrades norleucine and Bogosian et al. teaches expression of bovine somatotropin.

Therefore, the above references render claims 1-2, 8-11, 14-18, 42-43, and 47-48 *prima facie* obvious.

Claims 3-5 and 12 rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al., Bogosian et al. and Fenton et al. as applied to claims 1-2, 8-11, 14-18, 42-43, and 47-48 above, and further in view of Rice et al.

Claims 3-5 and 12 are drawn to a method of reducing the incorporation of non-standard amino acids into a bovine somatotropin in a microorganism by co-expressing in said microorganism said somatotropin and a non-standard amino acid degrading protein/glutamate dehydrogenase variant (K92L) comprising the amino acid sequence of ID NO:4 which is encoded by a sequence of SEQ ID NO: 3.

As discussed, above, it would have been obvious to one having ordinary skill in the art to reduce the incorporation of non-standard amino acid, norleucine, into a bovine somatotropin in a microorganism by co-expressing in said microorganism said somatotropin and a non-standard amino acid degrading protein/glutamate dehydrogenase variant (K92L). Further, Wang et al. teaches that lysine 89 (which corresponds to lysine 92 in *E. coli* glutamate dehydrogenase) is in the substrate binding site (page 5792).

The difference between the combined teachings of Wang et al., Bogosian et al. and Fenton et al. is that the reference to not each a non-standard amino acid degrading protein/glutamate dehydrogenase variant (K92L) comprising the amino acid sequence of ID NO:4 which is encoded by a sequence of SEQ ID NO: 3.

However, Rice et al. (FEMS Microbiol Rev. 1996 May;18(2-3):105-17 - form PTO-892) discloses a wildtype glutamate dehydrogenase isolated from *E. coli* (Figure 1 on page 107). Lysine at position 92 of wildtype *E. coli* glutamate dehydrogenase corresponds to the lysine residue at 89 of the glutamate dehydrogenase of Wang et al.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a K92L mutation in an *E. coli*

glutamate dehydrogenase in order to make an enzyme that degrades non-standard amino acids and use said mutant enzyme to reduce incorporation of heterologous proteins in *E. coli*.

One of ordinary skill in the art would have been motivated to use a mutant *E. coli* non-standard amino acid degrading protein/glutamate dehydrogenase since *E. coli* is used very often to express and produce heterolous proteins. One of ordinary skill in the art would have had a reasonable expectation of success since lysine 92(*E. coli*)/lysine 89 (*E. symbiosum*) is in the substrate binding pocket.

Therefore, the above references render claims 3-5 and 12 *prima facie* obvious.

### **Conclusion**

Claims 1-5, 8-12, 14-18, 42-43, and 47-48 are rejected.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

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you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/

Examiner, Art Unit 1652